REMARKS

Rejection of Claims 1-19 under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1-19 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention. The second paragraph of Section 112 requires that the claims set out and circumscribe a particular area which applicants regard as their invention with a *reasonable* degree of precision and particularity.

Specifically, the rejection alleges that Claims 1 and 10 are unclear about what disorder or disease is claimed, and that the antecedent basis for "its treatment" is unclear.

Claims 1 and 10 have been amended to clarify that the claims are directed to a method of alleviating a symptom of prostate cancer. With respect to the Examiner's comments that the symptoms listed in Claims 2-4 and 11-13 are not necessarily caused by cancer, Applicants submit that whether the symptoms can be caused by other conditions is not relevant to the examination of the claims. More specifically, while the symptoms listed in prior Claims 2-4 and 11-13 may be symptoms of other conditions, they are also symptoms of prostate cancer (see Background of the specification). Because the prostate gland encircles the urethra, problems with urination may occur if the enlargement of the prostate due to prostate cancer restricts urine flow through the tube. Such outflow obstruction can result in symptoms including urinary incontinence, urinary retention, urge-type dysfunction, unstable bladder, unstable sphincter, and recurrent urinary infection. Accordingly, these symptoms of prostate cancer can be alleviated using the botulinum toxin according to the present invention, and it is therefore submitted that the present claims are clear.

The Examiner is respectfully requested to reconsider the rejection under 35 U.S.C. § 112, second paragraph.

Objection to the Specification and Rejection of Claims 1-19 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-19 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). With this standard in mind, the rejections raised by the Examiner are discussed below.

The claims, as amended, are directed to a method of alleviating a symptom of prostate cancer, the method comprising the step of administering a therapeutic amount of a botulinum toxin into the prostate gland or a portion of the lower urinary tract of a patient with prostate cancer, thereby alleviating a symptom of prostate cancer. The specification teaches, at page 9, lines 22-24, that "[s]ymptoms of prostate cancer and conditions associated with prostate cancer may include pain." Applicant notes that it has been determined by the courts, that no working examples are required to enable a patent application. *In re Borkowski et al.*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). The specification, here, however, contains at least one working example, Example 3, acknowledged in the rejection to disclose treatment of a patient having prostate cancer with botulinum toxin, and the resulting relief from the symptom of pain. Thus, the specification discloses a correlation between treatment of prostate cancer with botulinum toxin and alleviating a symptom of prostate cancer (pain). Applicant submits that this correlation is sufficient to enable the claims, as described in detail below.

The rejection states that "the expectation that pain would be relieved for any and all prostate cancer patients as claimed would be unreasonable" due to "the age of the patient, complexity of his condition and treatments." Applicant disagrees with this analysis for two reasons. First, it is well

settled that the Examiner can not rely on general conclusions of "basic knowledge" or "common sense." Rather, evidence is required. *In re Lee*, 277 F.3d 1338, 1345-46 (Fed. Cir. 2002). In the present case, no evidence has been presented to support the assertions that the patient's age, complexity of his condition and treatments would have any effect on the efficacy of botulinum toxin with regard to relief of pain associated with the cancer.

Second, Applicant is not required to show efficacy of the treatment to the degree noted in the rejection. As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). This is true, even when the evidence is in the form of *in vitro* or *in vivo* animal model example; in the present case, however, a human example is shown. Applicant submits, therefore, that Example 3 provides a reasonable correlation between the use of botulinum toxin and alleviating a symptom of prostate cancer.

Regarding Examples 7-9, which the rejection has characterized as prophetic examples, the rejection reasons that "one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention" in part, because the results of Examples 7-9 are not shown. Applicant submits that this standard is inappropriate. Examples 7-9 describe protocols to be undertaken in studies or trials with human patients. In the situation where human clinical trials have been initiated for a therapeutic product or process, it should be presumed that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility. See MPEP § 2107.03 (emphasis in original). Thus, Examples 7-9 further support the conclusion of a reasonable correlation of therapeutic use.

The rejection further states that "the state of the art teaches that 'large controlled trials are absolutely required to establish the role of botulinum-A toxin injections in the fields of urology and neuroulology on evidence based medicine,'" in support of the finding of nonenablement. Again, Applicant submits that this standard is in inappropriate, as is confuses the standards for patentability with the requirements of FDA approval. FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws, *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir.

1995) (citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994)), nor is an applicant required to demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans. MPEP § 2107.01 and cases cited therein. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. It is improper to request evidence regarding the degree of effectiveness. MPEP § 2107.03 and cases cited therein (emphasis in original.) Applicant submits, therefore, that the fact that further testing will be needed to meet the requirements for drug approval has no bearing on the enablement analysis.

The rejection also reasons that the treatment or cure of prostate cancer with botulinum toxin, which acts as blocker of acetylcholine release from nerve endings and blocks neural transmission, is unpredictable because prostate cancer is not a neurological disorder. Further, the rejection states that "botulinum toxin primary affects neurological function but not prostate cancer." Applicant respectfully points out that because something has not previously been done is not a sufficient basis for rejecting an application that discloses how to do it. *In re Wooddy*, 331 F.2d 636, 639, 141 USPQ 518, 520 (CCPA 1964). In the present application, the inventors have discovered that is it possible to use botulinum toxin to treat prostate cancer, and in one respect, this treatment alleviates pain, a symptom associated with prostate cancer.

Moreover, as discussed above, the prostate enlarges in prostate cancer, and because the prostate gland encircles the urethra, problems with urination may occur if the gland's enlargement due to prostate cancer restricts urine flow through the tube. Such outflow obstruction may result in symptoms associated with the prostate cancer including urinary incontinence, urinary retention, urge-type dysfunction, unstable bladder, unstable sphincter, and recurrent urinary infection. The present specification, through working examples, demonstrates that botulinum toxin reduces prostate enlargement (*e.g.*, Examples 1 and 2) and alleviates urinary incontinence, pelvic pain, and unstable bladder (*e.g.*, Example 3).

Furthermore, the enclosed post-filing publication by Michl and Gress demonstrates that solid tumors may be treated with bacterial toxins (Michl and Gress, *Curr Cancer Drug Targets* 2004 4:689-702). Michl and Gress discuss the use of genetically modified bacteria and their toxins

targeting to surface molecules overexpressed in various tumors as a promising new treatment strategy in refractory cancers. Thus, a general correlation between the use of toxins and the treatment of cancers has been established. Applicant has provided evidence that botulinum toxin can be used to treat prostate cancer, in particular by providing a working example showing the alleviation of at least one symptom in a patient with prostate cancer.

Applicant provides further evidence regarding enablement in the form of two additional post-filing publications. Geurcini, et al., *Eur. Urol. Suppl.* 2005 4:150 and Geurcini, et al., *European Association of Urology (EAU) 20th Congress*, March 16-19 (2005), Istanbul, Turkey. These publications are submitted as further evidence that the present application was enabled as of its filing date. These references show improvement of symptoms in patients with BPH or adenocarcinoma (*e.g.*, a prostate cancer) after intraprostatic injection of botulinum toxin. The demonstrated improvements include reduction of prostate weight, reduction of PSAt, and decrease of urinary retention, for example. These are some of the symptoms that can arise from prostate cancer, as discussed in the specification (see Background). Therefore, it is clear from these references that botulinum toxin could be used effectively in the treatment of prostate cancer (in the alleviation of symptoms associated with prostate cancer). Indeed, these authors conclude (see Conclusions) that botulinum toxin is an "alternative to surgery in high grade voiding dysfunction, for BPH or cancer, particularly in patients at risk" (emphasis added).

Finally, the rejection states that the effects and doses of various types of botulinum toxin in the method are not disclosed in the specification, and that one cannot correlate generic therapeutic amount of botulinum toxin B, C, D, E, F and G as claimed. Applicant submits again that this standard, requiring a rigorous or an invariable exact correlation, and requiring evidence of the degree of effectiveness, is inappropriate. Instead, a reasonable correlation is all that is required. U.S. Patent No. 5,837,265 (of record) teaches that various types of botulinum toxin (classified into seven serotypes, A through G, on the basis of the immunological properties) have similar structure and pharmacological actions (see U.S. Patent No. 5,837,265, col. 1, lines 56-60). It is known that all of the botulinum toxins types A-G cleave cellular protein substrates which are involved in the release of the acetylcholine neurotransmitter into the synaptic cleft of neurons in the peripheral cholingergic nervous system. Applicant submits, therefore, that the pharmacological similarity of botulinum toxin

B, C, D, E, F and G to botulinum toxin A provides a reasonable correlation of the toxins' pharmacological activity.

In summary, Applicant has provided a specification which describes the treatment of prostate cancer with botulinum toxin through a detailed description of the invention and working examples. The description provides a reasonable correlation between the disclosed methods and the claimed subject matter. The application of safety and efficacy standards for pharmaceutical-type inventions is not required, and is contrary to established case law. Applicant therefore submits that the pending claims are fully enabled and respectfully requests reconsideration.

Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned at (303) 863-9700.

This statement constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-1970, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-1970.

Respectfully submitted,

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